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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/077,615	10/23/98	ARGUELLO R	740380CSA

EXAMINER	
EINSMANN, J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/077,615	ARGUELLO ET AL.	
	Examiner	Art Unit	
	Juliet C. Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *20 April 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9, 18-19, and 29-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 18-19, and 29-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's traversal of the restriction requirement filed 4/20/2000 (paper number 11) is found to be persuasive and therefore the restriction requirement is withdrawn. Claims 1-9, 18-19, and 29-30 are pending and have been examined herein.

Specification

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-1.825 because the specification recites sequences (See, for example, p. 35), however there is not sequence listing and no CRF has been submitted. Applicant is required to submit a CRF and paper copy of the Sequence Listing containing these sequences, in addition to any other sequences recited in the specification, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-9, 18-19 and 29-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9 are indefinite over the recitation of "separating the duplexes" because it is not clear if this separation is meant to encompass separation of the duplexes from one another or separating all duplexes from the rest of the solution.

Claims 2-9 are indefinite because it is not clear how they are intended to be related to the process steps of claim 1. It is not clear if the steps listed are intended to be in addition to those listed in claim 1 or if they are intended to be recited instead of those in claim 1. If applicant merely intends to recite dependent claims which only share a preamble with claim 1 this should be clarified.

Claims 4-5 are indefinite because it is not clear the recovering of the strands occurs instead of steps (iii) and (iv) of the previous claims somehow these steps are meant to occur in combination with those recited in claims 2 and 3.

Claims 18-19 and 29-30 are indefinite for failing to recite a final process step which agrees back with the preamble. For example, claims 18-19 are drawn to a method for determining whether a prospective recipient in a tissue or organ transplant operation has alleles of a gene that are compatible with the alleles of a prospective donor in the operation, yet the claims recite a final step selected from: comparing positions, sequencing, SSP amplification analysis or SSO analysis. The claims do not set forth the relationship between the comparing positions, sequencing, SSP amplification analysis or SSO analysis and the determining whether a prospective recipient in a tissue or organ transplant operation has alleles of a gene that are compatible with the alleles of a prospective donor in the operation and therefore, it is not clear whether the claims are intended to be drawn to a method for determining whether a prospective recipient in a tissue or organ transplant operation has alleles of a gene that are compatible with

the alleles of a prospective donor in the operation or a method for comparing positions, sequencing, SSP amplification analysis or SSO analysis.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1, 2, and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Wu (US 5387505).

Wu teaches a method for separating a DNA molecule from a mixture of DNA molecules, which method comprises:

(i) amplifying the DNA moleuclues in the mixture (Col. 11, lines 20-22);

(ii) hybridizing single strands of the amplified DNA molecules with a complementary strand of a reference DNA molecule so as to form duplexes (Col. 11, lines 34-40); and

(iii) separating the duplexes (Col. 11, lines 47-49).

Wu further teaches a method for separating a DNA molecule from a mixture of DNA molecules, which method comprises:

(i) amplifying the DNA molecules in the mixture employing a pair of primers in which one of the primers has a ligand molecule attached (Col. 9, lines 21-30, 47-55);

(ii) contacting the amplified mixture of double stranded DNA molecules with an receptor on solid support under conditions such that the biotin binds the avidin (Col. 9, lines 56-63);

(iii) separating the mixture of double-stranded DNA molecules into single-strands and removing the strands that are not bound to the support by the ligand (Col. 10, lines 1-8);

(iv) recovering the remaining strands from the solid support (Col. 10, lines 9-17);

(v) mixing the recovered strands with a complementary strand of a reference DNA molecule so as to form duplexes (Col. 11, lines 34-40); and

(vi) separating the duplexes (Col. 11, lines 47-49).

With regard to claim 6, biotin is considered to be a high molecular weight molecule.

7. Claims 1 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Gudibande *et al.* (US 5597910).

Gudibande *et al.* teach a method for separating a DNA molecule from a mixture of DNA molecules, which method comprises:

(i) amplifying a single strand of each of the DNA molecules in the mixture (Col. 23, lines 45-51);

(ii) mixing the amplified single strands with a complementary strand of a reference DNA molecule so as to form duplexes (Col. 23, lines56-58); and

(iii) separating the duplexes (Col. 23, lines 58-61).

8. Claims 1 and 29-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimmerman (Nucleic Acids Research, 1993, Vol. 21, No. 19, 4541-4547).

Zimmerman *et al.* teach a method for identifying a DNA molecule, which method comprises:

(i) contacting the DNA molecule with a labeled reference DNA strand under conditions such that the reference strand hybridizes to a complementary strand of the DNA molecule so as to form a test duplex (p. 4542, heading "DHDA");

(ii) running the test duplex and one or more control duplexes in a gel by electrophoresis (p. 4542, heading "DHDA"); and

(iii) comparing the position of the test duplex on the gel with the position of the control duplexes (p. 4543 and Fig. 2).

In the method taught by Zimmerman *et al.* the control duplexes are duplexes which have graded mobilities and which are run in a different lane on the gel to the test duplex. Zimmerman *et al.* specifically teach that "every DQA1 allele, with the exception of DQA1*0601 can be distinguished by the unique mobility of one or both of its HD bands.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu.

Wu teaches a method for separating a DNA molecule from a mixture of DNA molecules, which method comprises:

(i) amplifying the DNA molecules in the mixture employing a pair of primers in which one of the primers has a ligand molecule attached (Col. 9, lines 21-30, 47-55);

(ii) contacting the amplified mixture of double stranded DNA molecules with an receptor on solid support under conditions such that the biotin binds the avidin (Col. 9, lines 56-63);

(iii) separating the mixture of double-stranded DNA molecules into single-strands and removing the strands that are not bound to the support by the ligand (Col. 10, lines 1-8);

(iv) recovering the remaining strands from the solid support (Col. 10, lines 9-17);

(v) mixing the recovered strands with a complementary strand of a reference DNA molecule so as to form duplexes (Col. 11, lines 34-40); and

(vi) separating the duplexes (Col. 11, lines 47-49).

With regard to claim 7, biotin is considered to be a high molecular weight molecule.

Wu does not explicitely teach that the complementary strand of reference DNA is generated by amplification with a primer which carries a ligand, however, Wu does teach a method for preparing a single-stranded DNA comprising

(i) amplifying the reference DNA molecule employing a pair of primers in which one of the primers carries a ligand, so as to produce amplified double-stranded reference DNA molecule in which one of the strands carries a ligand (Col. 3, lines 5-9);

(ii) contacting the amplified mixture of double stranded DNA molecules with an receptor on solid support under conditions such that the biotin binds the avidin (Col. 3, lines 11-16);

(iii) separating the mixture of double-stranded DNA molecules into single-strands and removing the strands that are not bound to the support by the ligand (Col. 3, lines 17-18); and

(iv) recovering the remaining strands from the solid support (Col. 3, lines 24-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used this method taught by Wu for the production of the

complementary reference strand for use in a hybridization assay. The ordinary practitioner would have been motivated to use this method instead of, for example, chemical synthesis, since Wu teaches that this method "avoids the harsh chemical denaturing conditions that are described in the literature, and yet the need for preparing or purchasing expensive biotinylated reagents is also avoided (Col. 3, lines 28-31)."

11. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu as applied to claim 3 above, and further in view of Biomagnetic Techniques in Molecular Biology, section 10.1, p. 116 (Dynal, 1995).

The teachings of Wu are applied to these claims as discussed in the rejections of claims 3 and 7 above. Wu does not teach a step in which the strands not bound to the support are recovered.

However, such a method was routinely used in the art as a method of isolating a single stranded nucleic acid, as is exemplified in the Biomagnetic Techniques in Molecular Biology manual, in figure 10.1 (p. 116).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the method exemplified in the Biomagnetic techniques manual in the method of Wu in and thus to have provided an equally effective means by which to isolate a single stranded nucleic acid, since the manual teaches that such a method "enables purificatoin of single-stranded templates and elution of single-stranded labeled probes without contamination of unlabeled complementary DNA (p. 116)."

12. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gudibande *et al.* (US 5597910).

Gudibande *et al.* teach a method for separating a DNA molecule from a mixture of DNA molecules, which method comprises:

(i) amplifying a single strand of each of the DNA molecules in the mixture (Col. 23, lines 45-51);

(ii) mixing the amplified single strands with a complementary strand of a reference DNA molecule so as to form duplexes (Col. 23, lines56-58); and

(iii) separating the duplexes (Col. 23, lines 58-61).

Gudibande *et al.* do not teach methods in which single stranded amplification is used to produce the complementary reference strand. However, in light of the teachings of Gudibande *et al.* concerning the use and effectiveness of such a methodology, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used such an amplification method as an alternative to chemical synthesis of probes, since such a method would have been expected to be equally effective for the production of complementary single stranded probes.

13. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu in view of Zimmerman *et al.*

Wu teaches a method for separating and identifying a nucleic acid, which method comprisies:

Wu further teaches a method for separating a DNA molecule from a mixture of DNA molecules, which method comprises:

(i) amplifying the DNA molecules in the mixture employing a pair of primers in which one of the primers has a ligand molecule attached (Col. 9, lines 21-30, 47-55);

(ii) contacting the amplified mixture of double stranded DNA molecules with an receptor on solid support under conditions such that the biotin binds the avidin (Col. 9, lines 56-63);

(iii) separating the mixture of double-stranded DNA molecules into single-strands and removing the strands that are not bound to the support by the ligand (Col. 10, lines 1-8);

(iv) recovering the remaining strands from the solid support (Col. 10, lines 9-17);

(v) mixing the recovered strands with a complementary strand of a reference DNA molecule so as to form duplexes (Col. 11, lines 34-40); and

(vi) separating the duplexes (Col. 11, lines 47-49).

Wu does not specifically teach steps in which the separation of the duplexes occurs bia gel electrophoresis and in which a comparison of the positions to which a duplex migrates on the gel is carried out.

Zimmerman *et al.* teach methods of HLA typing which employ heteroduplex analysis, including running hybridization samples on a gel and comparing the location of different heteroduplexes for the identification of a patient's HLA type. In the method taught by Zimmerman *et al.* the control duplexes are duplexes which have graded mobilities and which are run in a different lane on the gel to the test duplex. Zimmerman *et al.* specifically teach that "every DQA1 allele, with the exception of DQA1*0601 can be distinguished by the unique mobility of one or both of its HD bands. "

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the methods taught by Wu and Zimmerman *et al.* in order to have developed a method for determining whether a prospective recipient in a tissue or organ transplant has alleles of a gene that are compatible with the alleles of a prospective donor in the

operation since Wu teaches that his method "is particularly desirable to amplify Human Leukocyte Antigen (HLA) DNA (Col. 8, lines 44-45)" and Zimmerman *et al.* teach that their heteroduplex analysis method has numerous advantages over other typing methods such as SSO-typing, for example the use of less probes, the ability to produce results under low stringency, and the simultaneous positive identification of multiple alleles following a single probe hybridization (p. 4545).

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1655

June 15, 2000